PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 1692.258WO1	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/US2004/043571	International filing date *(day/month/year)* 22.12.2004	Priority date *(day/month/year)* 22.12.2003
International Patent Classification (IPC) or national classification and IPC C07D473/16, C07D473/18, A61K31/52		
Applicant GILEAD SCIENCES, INC. et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 7 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand 24.10.2005	Date of completion of this report 06.03.2006
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Cortés, J Telephone No. +49 89 2399-8206

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2004/043571

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:

   ☐ international search (under Rules 12.3 and 23.1(b))
   ☐ publication of the international application (under Rule 12.4)
   ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

2-41	as originally filed
1	received on 31.10.2005 with letter of 24.10.2005

Claims, Numbers

36-47	as originally filed
1-35	received on 31.10.2005 with letter of 24.10.2005

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:

   ☐ the description, pages
   ☐ the claims, Nos.
   ☐ the drawings, sheets/figs
   ☐ the sequence listing *(specify)*:
   ☐ any table(s) related to sequence listing *(specify)*:

4. ☒ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

   ☐ the description, pages
   ☒ the claims, Nos. 1
   ☐ the drawings, sheets/figs
   ☐ the sequence listing *(specify)*:
   ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2004/043571

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 23-28

because:

☒ the said international application, or the said claims Nos. 23-28 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2004/043571

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	5,6,9-15
	No:	Claims	1-4,7,8,16-35
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-35
Industrial applicability (IA)	Yes:	Claims	1-22, 29-35
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Re Item I
Basis of the opinion

With letter of 24.10.2005 the Applicant has filed an ameded claim set.

New claim 1 has been amended by a proviso aimed at excluding the compounds of D1. D1 is not a so-called "accidental" disclosure but represents the closest prior art.

This proviso has no basis in the application as originally filed. Therefore new claim 1 represents added matter and consequently contravenes Article 34(b) PCT.

Claim 1 has therefore been examined as if this amendment had not been made.

Re Item III
Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 23-28 relate to subject matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V
Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The following documents have been cited in the International Search Report:

D1: KATO ET AL: "Enantio- and diastereoselective synthesis of 4?-substituted carbocyclic nucleosides" TETRAHEDRON, vol. 9, no. 6, 1998, pages 911-914, XP002328141

D2: DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 1999, KATO, KEISUKE ET AL: "Stereoselective synthesis of 4'-.alpha.-alkylcarbovir derivatives based on an asymmetric synthesis or chemo-enzymatic

procedure" XP002328143 retrieved from STN Database accession no. 1999:614511

D3: KO ET AL: "Efficient synthesis of novel carbocyclic nucleosides via sequential Claisen rearrangement and ring-closing metathesis" TETRAHEDRON LETTERS, vol. 43, no. 36, 2002, pages 6399-6402, XP002328182

D4: US-A-6 072 053 (VINCE ET AL) 6 June 2000 (2000-06-06)

D5: ROBERT S M: "DEVELOPMENT OF THE ROUTE TO THE NEW ANTI-AIDS DRUG ABACAVIR: A HIGHLIGHT OF ACADEMIC/INDUSTRY LIAISON" IDRUGS, CURRENT DRUGS LTD, GB, vol. 1, no. 8, 1998, pages 896-899, XP008044472 ISSN: 1369-7056

D6: WO 02/100415 A (HOFFMANN-LA ROCHE) 19 December 2002 (2002-12-19)

D7: US-A-5 750 343 (MAAG) 12 May 1998 (1998-05-12)

Novelty (Article 33(2) PCT)

D1 and D2 disclose compounds which are encompassed by the present claim set.

The claims 1-4,7,8 and 16-35 are therefore not novel.

The present compounds differ from the compounds in D3 in that R1 is unsubstituted, from the compounds in D4 and D5 in R1, from the compounds in D6 in the double bond of the cyclopenten and from the compounds in D7 in the cyclopenten.

Inventive Step (Article 33(3) PCT)

D1 to D7 disclose antiviral modified nucleosides. D1 could be regarded as the closest prior art.

The problem of the invention was the provision of new antiviral compounds.

Since D1 and D2 already disclose antiviral compounds within the present scope, the present application lacks an inventive step.

In the above mentioned letter the Applicant alleges that the Application would be based on an inventive step, since D1 does not disclose any biological data and D2 reports that the compounds disclosed therein "exhibited no aniviral activity against HIV-1" and that a skilled person would therefore not have been motivated to prepare any derivatives of the compounds disclosed in D1 or D2.

The examiner disagrees. Both D1 and D2 explicitely disclose potential antiviral agents (D1: e.g. 1st paragraph and documents 4 and 5 cited in D1; D2: e.g. "the effect of the further structural modification on the antiviral activity in this series need to be investigated"). A skilled person would have therefore been motivated to investigate the antiviral activity of the compounds disclosed therein and derivatives of these compounds.

Clarity (Article 6 PCT) and Remarks

Some substituents for B have been listed more than one time in claims 1 and 3 (e.g. 7-deazaguanine).

The two patents seem to have been cited with a wrong publication number (present description, page 1, line 12).

Re Item VI
Certain documents cited

Reference is made to the following documents:

D8: HEGEDUS ET AL: "Synthesis of 4'-Methyl and 4'-Cyano Carbocyclic 2',3'-Didehydro Nucleoside Analogues via 1,4-Addition to Substituted Cyclopentenones" JOURNAL OF ORGANIC CHEMISTRY, vol. 69, no. 24, 30 October 2004 (2004-10-30), pages 8492-8495, XP002328142

D9: WO 2005/011709 A (YALE UNIVERSITY) 10 February 2005 (2005-02-10)

The priority documents pertaining to the present application were not available at the time of establishing this report. Hence, it is based on the assumption that all claims enjoy priority rights from the filing date of the priority document. If it later turns out that this is not correct, D8 and D9 could become relevant to asses whether the present claims satisfy the criteria set forth in Article 33(1) PCT.

4' SUBSTITUTED CARBOVIR-AND ABACAVIR-DERIVATIVES AS WELL AS RELATED COMPOUNDS WITH HIV AND HCV ANTIVIRAL ACTIVITY

PRIORITY OF INVENTION

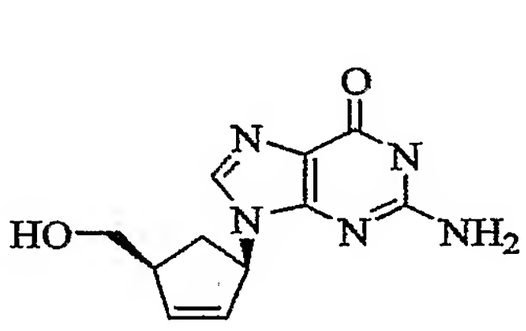
This application claims the benefit of priority under 35 U.S.C. § 119(e) to U.S. Provisional Patent Application Serial Number 60/532,256, filed 22 December 2003. The entirety of this Provisional Application is incorporated herein by reference.

FIELD OF THE INVENTION

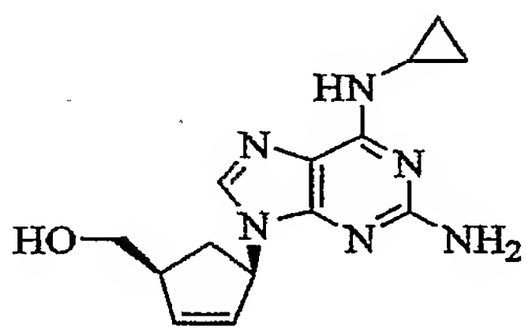
The invention relates generally to 4'-substituted nucleoside derivatives with antiviral activity.

BACKGROUND OF THE INVENTION

Carbovir along with abacavir are well known anti-HIV carbocyclic nucleosides. Abacavir is the most potent nucleoside reverse transcriptase inhibitor (NRTI) developed to date. An average reduction in viral load of more than 1.4 log10 RNA copies/ml is observed after a short course of abacavir monotherapy.



Carbovir



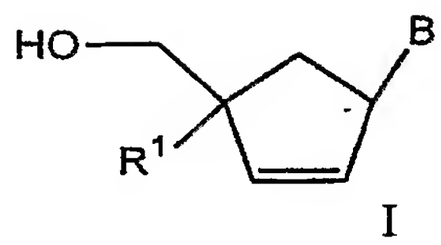
Abacavir

Dideoxynucleotide use such as dideoxycytidine (ddC) and of didehydrodideoxythymidine (d4T) is limited by associated painful sensory-motor peripheral neuropathy. Dideoxyinosine also shares this complication as well as causing acute pancreatitis, and hepatotoxicity in some cases (Maag, H. et al., *J. Med. Chem.*, **1992**, *35*, 1440). Yet another concern about this class of compounds has been the emergence of resistant HIV strains in patients undergoing treatment with nucleosides. For instance the ddI-resistant strains were also shown to be resistant to ddC. In another study, clinical HIV isolates

Claims

What is claimed is:

1. A compound of Formula I:



I

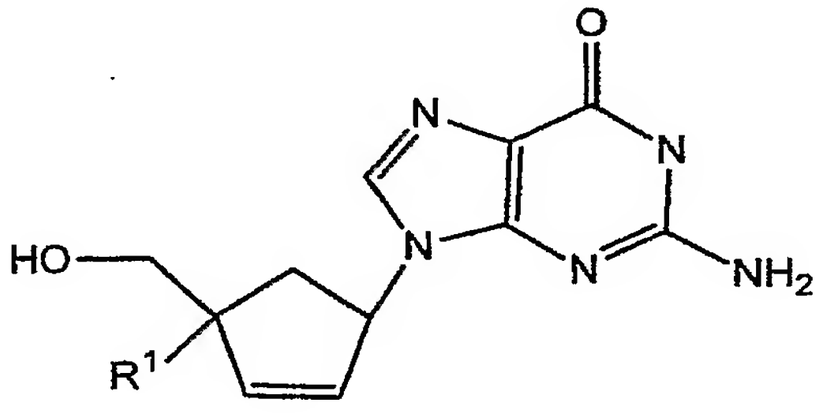
wherein:

B is adenine, guanine, cytosine, uracil, thymine, 7-deazaadenine, 7-deazaguanine, 7-deaza-8-azaguanine, 7-deaza-8-azaadenine, inosine, nebularine, nitropyrrole, nitroindole, 2-aminopurine, 2-amino-6-chloropurine, 2,6-diaminopurine, hypoxanthine, pseudouridine, pseudocytosine, pseudoisocytosine, 5-propynylcytosine, isocytosine, isoguanine, 2-thiopyrimidine, 6-thioguanine, 4-thiothymine, 4-thiouracil, O^6-methylguanine, N^6-methyladenine, O^4-methylthymine, 5,6-dihydrothymine, 5,6-dihydrouracil, 4-methylindole, triazole, or pyrazolo[3,4-d]pyrimidine; and B is optionally substituted with one or more alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, hydroxy, or halo; and

R^1 is alkyl, alkenyl, alkynyl, cyano, azido, or fluoromethyl;

or a pharmaceutically acceptable salt or solvate thereof;

provided the compound of formula I is not a compound of formula II:



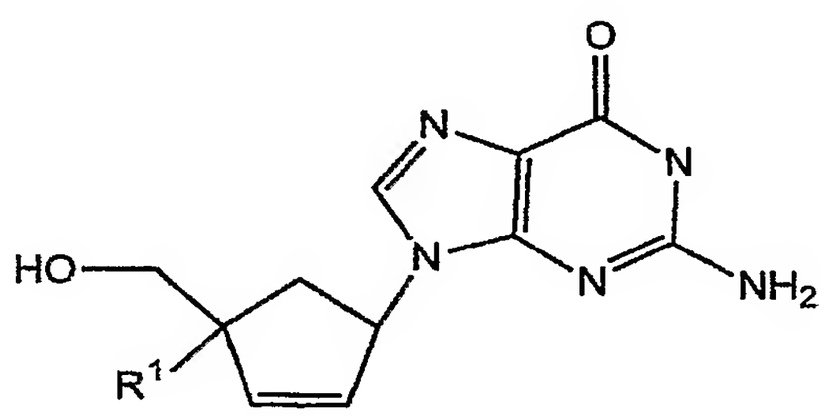
wherein R^1 is alkyl.

2. The compound of claim 1 wherein B is adenine, guanine, cytosine, uracil, or thymine; which B is optionally substituted with one or more alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, hydroxy, or halo.

3. The compound of claim 1 wherein B is 7-deazaadenine, 7-deazaguanine, 7-deaza--azaguanine, 7-deaza-8-azaadenine, inosine, nebularine, nitropyrrole, nitroindole, 2-aminopurine, 2-amino-6-chloropurine, 2,6-diaminopurine, hypoxanthine, pseudouridine, pseudocytosine, pseudoisocytosine, 5-propynylcytosine, isocytosine, isoguanine, 7-deazaguanine, 2-thiopyrimidine, 6-thioguanine, 4-thiothymine, 4-thiouracil, O^6-methylguanine, N^6-methyladenine, O^4-methylthymine, 5,6-dihydrothymine, 5,6-dihydrouracil, 4-methylindole, triazole, or pyrazolo[3,4-d]pyrimidine; and B is optionally substituted with one or more alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, hydroxy, or halo

4. The compound of claim 1 wherein B is adenine, guanine, cytosine, uracil, or thymine.

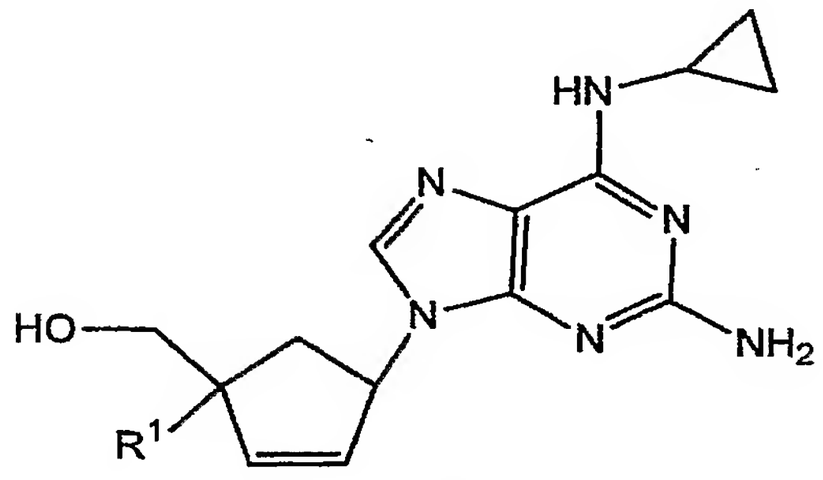
5. The compound of claim 1 which is a compound of formula II:



II

wherein R^1 is alkenyl, alkynyl, cyano, azido, or fluoromethyl.

6. The compound of claim 1 which is a compound of formula III:



III

wherein R^1 has any of the values defined in claim 1.

7. The compound of any one of claims 1-6 wherein R^1 is alkyl.

8. The compound of any one of claims 1-6 wherein R^1 is methyl.

9. The compound of any one of claims 1-6 wherein R^1 is fluoromethyl.

10. The compound of any one of claims 1-6 wherein R^1 is alkenyl.

11. The compound of any one of claims 1-6 wherein R^1 is vinyl.

12. The compound of any one of claims 1-6 wherein R^1 is alkynyl.

13. The compound of any one of claims 1-6 wherein R^1 is ethynyl.

14. The compound of any one of claims 1-6 wherein R^1 is cyano.

15. The compound of any one of claims 1-6 wherein R^1 is azido.

16. A pharmaceutical composition, comprising an effective amount of a compound of Formula I as described in any one of claims 1-15, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient.

17. A pharmaceutical composition comprising an effective amount of a compound of Formula I as described in any one of claims 1-15, or a pharmaceutically acceptable salt or solvate thereof; a pharmaceutically acceptable excipient; and a therapeutically effective amount of another therapeutic agent.

18. The pharmaceutical composition of claim 16 which further comprises an AIDS treatment agent selected from an HIV inhibitor agent, an anti-infective agent, and an immunomodulator.

19. The pharmaceutical composition of claim 16 which further comprises an HIV-protease inhibitor.

20. The pharmaceutical composition of claim 16 which further comprises a reverse transcriptase inhibitor.

21. The pharmaceutical composition of claim 16 which further comprises a non-nucleoside reverse transcriptase inhibitor.

22. The pharmaceutical composition of claim 16 which further comprises an HIV integrase inhibitor.

23. A method of inhibiting a viral infection in an animal (e.g. a mammal), comprising administering to the animal, an effective amount of a compound of Formula I as described in any one of claims 1-15, or a pharmaceutically acceptable salt or solvate thereof.

24. A method for the treatment or prevention of the symptoms or effects of a viral infection in an animal comprising administering to the animal, an effective amount of a

compound of Formula I as described in any one of claims 1-15, or a pharmaceutically acceptable salt or solvate thereof.

25. A method of inhibiting an HCV infection in an animal comprising administering to the animal, an effective amount of a compound of Formula I as described in any one of claims 1-15, or a pharmaceutically acceptable salt or solvate thereof.

26. A method for the treatment or prevention of the symptoms or effects of HCV infection in an infected animal comprising administering to the animal, an effective amount of a compound of Formula I as described in any one of claims 1-15, or a pharmaceutically acceptable salt or solvate thereof.

27. A method of inhibiting a viral enzyme comprising contacting a sample suspected of containing viral infected cells or tissues with an effective amount of a compound of Formula I as described in any one of claims 1-15, or a pharmaceutically acceptable salt or solvate thereof.

28. A method of inhibiting RNA-dependent RNA polymerase in an animal comprising administering to the animal, an effective amount of a compound of Formula I as described in any one of claims 1-15, or a pharmaceutically acceptable salt or solvate thereof.

29. A compound of Formula I as described in any one of claims 1-15, or a pharmaceutically acceptable salt or solvate thereof, for use in medical therapy.

30. The use of a compound of Formula I as described in any one of claims 1-15, or a pharmaceutically acceptable salt or solvate thereof, to prepare a medicament useful for inhibiting a viral infection in an animal.

31. The use of a compound of Formula I as described in any one of claims 1-15, or a pharmaceutically acceptable salt or solvate thereof, to prepare a medicament useful for the treatment or prevention of the symptoms or effects of a viral infection in an animal.

32. The use of a compound of Formula I as described in any one of claims 1-15, or a pharmaceutically acceptable salt or solvate thereof, to prepare a medicament useful for inhibiting an HCV infection in an animal.

33. The use of a compound of Formula I as described in any one of claims 1-15, or a pharmaceutically acceptable salt or solvate thereof, to prepare a medicament useful for the treatment or prevention of the symptoms or effects of HCV infection in an infected animal.

34. The use of a compound of Formula I as described in any one of claims 1-15, or a pharmaceutically acceptable salt or solvate thereof, to prepare a medicament useful for inhibiting an RNA-dependent RNA polymerase in an animal.

35. A process for making a pharmaceutical composition comprising combining a compound of Formula I as described in any one of claims 1-15, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient.